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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/160,965	12/02/1993	JAMES M. MUSSER	06239007001	2506

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/160,965	MUSSER ET AL.	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-47* is/are pending in the application.

4a) Of the above claim(s) *36-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-35 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on May 8, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/160,965 is acceptable and a CPA has been established. An action on the CPA follows.

Amendment Entry

2. The amendment filed October 29, 2001 has been entered. Claim 3 has been cancelled. Claims 1 and 4-6 have been amended. Claims 20-47 have been newly added. Claims 1 and 4-47 are under consideration in this office action.

Election/Restrictions

3. Newly submitted claims 36-44 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are drawn to different products i.e., vaccines and isolated peptides which are distinct as determined by their different SEQ ID Numbers. The inventions are further distinct because they are comprised of a different structure when compared to the instant group.

The invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 36-44 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4-35 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a vaccine both with and without a pharmaceutically acceptable vehicle and method of immunizing comprising a cysteine protease comprising at least one amino acid substitution and said substitution occurs at positions 145, 185, 192, 340, 356 and 357. The written description, in this case, only sets forth the creation of mutated cysteine proteases employed to disrupt cysteine protease function and to map regions that constitute antigenic domains and not the combination of mutations or use in vaccines. See page 32 of the instant specification. The combination of specific amino acid mutations or their use in vaccines and associated methods of immunization have not been disclosed; and therefore the written description is not commensurate in scope with the claims drawn to a vaccine.

The instant specification fails to provide the identity of vaccines either with or without a pharmaceutically acceptable vehicle and method of immunizing comprising a

cysteine protease comprising at least one amino acid substitution and said substitution occurs at positions 145, 185, 192, 340, 356 and 357. There is no description of any vaccines comprised of such mutations. There is no teaching of the method steps required to immunize a mammal comprising said mutations in the cysteine protease. The instant specification fails to provide any experiments that show that the mutant protease vaccine comprised of any combination of the recited amino acid mutations would be effective in protecting a human or other animal against a Group A streptococcal bacterial infection. There is no teaching the specification that all six positions as recited in claims result in a mutant protease with the ability to confer immunity to a mammal as claimed. There is no data showing the incorporation of the recited amino acid substituted protease into a vaccine.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of using. The vaccine and methods themselves, along with comprising the recited mutations are required. Thus a precise description of the mutation comprised within the vaccine that confers immunity is necessary. Thus the specification is insufficient to support the instant claims

as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

In view of these considerations, a person skilled in the art would not have viewed the teachings of the specification sufficient to show that applicants were in possession of a vaccine comprising the mutated cysteine protease and method of immunizing as asserted in the specification as instantly claimed.

This is a new matter rejection

5. Applicants have added new claims drawn to vaccines both with and without a pharmaceutically acceptable vehicle and method of immunizing comprising a cysteine protease comprising at least one amino acid substitution and said substitution occurs at positions 145, 185, 192, 340, 356 and 357. Applicants point to figure 8 and pages 32-35 for support and enablement of the newly added claims. Figure 8 shows the processing sites, location of amino acid variations found in the proteins made by speB2 and speB4 alleles and amino acids that are targets for mutation. However, figure 9 does not show that any combination of amino acid substitutions in the cysteine protease comprised in a vaccine will confer immunity to a mammal against streptococcus infection. Furthermore, pages 32-35 of the instant specification fails to provide support for claimed vaccines. The amended claims create a new genera of combinations where the conception of "combinations" in all varieties is not set forth in the specification or original claims. Applicants fail to point to support by page and line number in the

instant specification, thus it appears that the amendment lacks support. Therefore, the claims are rejected for incorporating new matter.

6. Claims 1, 4-35 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a vaccine both with and without a pharmaceutically acceptable carrier and method of immunizing comprising a cysteine protease comprising at least one amino acid substitution and said substitution occurs at positions 145, 185, 192, 340, 356 and 357.

The specification, in example 20, teaches the creation of mutant speB proteins. See the specification at pages 32-34. However, the specification fails to teach vaccine examples comprised of the recited mutated cysteine protease comprising at least one but not limited to comprising mutations at all six positions. There is no teaching the specification that all six positions as recited in claims result in a mutant protease with the ability to confer immunity to a mammal as claimed. The instant specification fails to provide any experiments that show that the mutant protease vaccine comprised of any combination of the recited amino acid mutations would be effective in protecting a human or other animal against a Group A streptococcal bacterial infection. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to a bacterial infection or disease induction. The vaccine art is highly unpredictable and

the instant specification fails to provide any information that the recited vaccine comprising any combination of the amino acid mutations would provide any immunity to any type of patient against the streptococcal bacterial infection. There are no immunological experiments provided to demonstrate that the claimed vaccines are capable of mounting an effective immune response and more importantly, there are no challenge experiments to demonstrate that an animal immunized with any of the mutant proteases would be protected from infection.

There are no protocols provided which demonstrate that the mutated proteases would be effective in immunization, nor are their protocols detailing the amount of mutant cysteine protease needed to mount a sufficient immune response. There is no teaching as to what the most effective route of administration for the claimed vaccines. There is merely a general outline of vaccines that do not apply directly to the instant invention. It is unclear that one of skill in the art could follow these general guidelines and achieve immunization against a streptococcal infection. The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity streptococcal infection and/or disease. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing an infection. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced against Group A streptococcus.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies" (page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful attenuated live or whole cell vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach the identity a mutated cysteine protease comprised of any of the possible combinations of amino acid mutation within a vaccine or used in a method of immunization. Furthermore, the specification fails to adequately disclose a description of the claimed vaccines, thus a skilled artisan would be required to de novo locate, identify and characterize the claimed vaccines with the recited mutations. Moreover, the specification lacks examples of representative mutated cysteine proteases comprised within a vaccine. Accordingly, this would require undue experimentation given the fact that the specification is completely lacking in teachings as vaccines with the claimed mutations. Thus, the art indicates that it would require

undue experimentation to formulate and use a successful vaccine and method of immunization without the prior demonstration of vaccine efficacy.

The claims are directed to vaccines both with and without a pharmaceutically acceptable vehicle and method of immunization; however, the instant specification fails to provide any experiments that show that such vaccines would be effective in establishing resistance against streptococcal bacteria in a mammal without the use of an adjuvant. The vaccine art is highly unpredictable and the instant specification fails to provide any information that the recited cysteine protease vaccine without the use of an adjuvant would provide immunity to a streptococcal infection.

There are no protocols provided which demonstrate the mutant protease comprised of any combination of amino acid substitutions in vaccine form would be effective in establishing immunity without the use of an adjuvant. It is unclear that one of skill in the art could follow these guidelines of the specification and establish immunity against streptococcal bacteria using the mutant protease vaccine without an adjuvant. The specification does not provide substantive evidence that the claimed vaccines are capable of establishing immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of establishing immunity to the streptococcal bacterium. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if resistance has been established against the bacterium using a vaccine without an adjuvant.

Absent clear demonstration of the production of a mutated cysteine protease vaccine comprised pf any combination of amino acid substitutions without the incorporation of an adjuvant, the vaccine could not be used in any well-established manner for eliciting protection against streptococcal bacteria. In absence of further guidance from applicants, the skilled artisan would have to discover what the appropriate substrate conditions are. Such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. Such need for non-routine experimentation demonstrates the specification is not enabled for the use of a mutated cysteine protease vaccine without an adjuvant. Accordingly, the specification lacks enablement for the asserted use of the vaccine without an adjuvant.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
July 24, 2002

MARK NAVARRO
PRIMARY EXAMINER